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Synthesis and Antitumor Activity of a New Dinuclear Platinum(II) Complex, Di-μ-sulfoacetato-bis[(1R,2R)-1,2-diaminocyclohexane]platinum(II)

Kojiro OKUDE, Hikaru ICHIDA, T. Ken MIYAMOTO,* Yukiyoshi SASAKI, and Tazuko TASHIRO†

Department of Chemistry, Faculty of Science, The Universtiy of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

†Cancer Chemotherapy Center, J. C. R., Kami-Ikebukuro, Toshima-ku, Tokyo 170

Di-μ-sulfoacetato-bis[(1R,2R)-1,2-diaminocyclohexane]-platinum(II), $[Pt(C_6N_2H_{14})]_2(CO_2CH_2SO_3)_2$, has been synthesized. The complex has a di-μ-carboxo bridged dinuclear structure and shows significant antitumor activity against mice leukemia L1210.

Since discovery of widespread antitumor activity of cis-platin, cis-dichloro-diammineplatinum(II), a number of platinum complexes have been synthesized as anticancer agents.[1] Among them there are promising compounds such as carbo-platin,[2] iproplatin,[3] and [(1R,2R)-1,2-diaminocyclohexane]platinum(II) derivatives.[4] Many of these compounds are, however, mononuclear complexes and few oligonuclear platinum complexes have shown the antitumor activity.[5]

In recent years, the formation of hydroxo-bridged di-,[6] or tri-nuclear[7] complexes have been reported in the hydrolysis reaction of cis-platin, and platinum oligomers such as "platinum blue"[8] have also come to much attention. These researches suggest an importance of oligonuclear species in the platinum chemistry, but antitumor activities have not been reported on these oligomers except a few examples.

We report here the synthesis and antitumor activity of a new dinuclear platinum complex, di-μ-sulfoacetato-bis[(1R,2R)-1,2-diaminocyclohexane]platinum(II).

Synthesis of the title compound: An aqueous solution of dinitrato[(1R,2R)-1,2-diaminocyclohexane]platinum(II) was passed through a column packed with the anion exchange resin (Diaion SA10AOH) and an equimolar amount of sulfoacetic acid (Aldrich) was added to the eluate. The reaction mixture was evaporated at ca. 50 °C under reduced pressure and the precipitate was recrystallized from H_2O (60-80% yield). Elemental analysis. Found: C; 19.70, H; 3.98, N; 5.84, S; 6.62%. Calcd for $Pt_2S_2O_{10}N_4C_{16}H_{32}.3H_2O$: C; 20.25, H; 4.04, N; 5.91, S; 6.76%. Solubility in water is ca. 5 mg cm^{-3} at room temperature.

An X-ray structure analysis[9] shows that the compound is a dinuclear complex, having di-μ-bridged carboxylate ligands (Fig. 1). Because of the poor coordination ability of the sulfonate ligand, mononuclear structure with six membered chelation of sulfoacetate ligand might be less stable than the dinuclear structure.

Antitumor activity of the complex against mice leukemia L1210 is listed in Table 1. From the mean survival times of treated (T) and control (C) mice, T/C

values are calculated as indicators of the activity. The title compound shows high activity, with many long-survivors, at relatively low dose conditions. The toxic dose is also somewhat higher than that of cis-platin.[4]

Judging from these results, the title complex offers an example to the antitumor potency of dinuclear platinum species.

Table 1. Antitumor Activity against Mice Leukemia L1210

Dose/ mg kg $^{-1}$	T/C (%)
50	Toxic
25	128 P[a)]
12.5	269 P (3)[b)]
6.25	230 P (1)

10^5 cells/mouse were transplanted i.p. into CDF_1 mice (6 mice/group) and sample was administered i.p. on days 1, 5, and 9.

a) T/C value over 125 was evaluated as antitumor active and indicated with P.

b) The numbers in parenthese indicate 30-days survivors out of 6 mice.

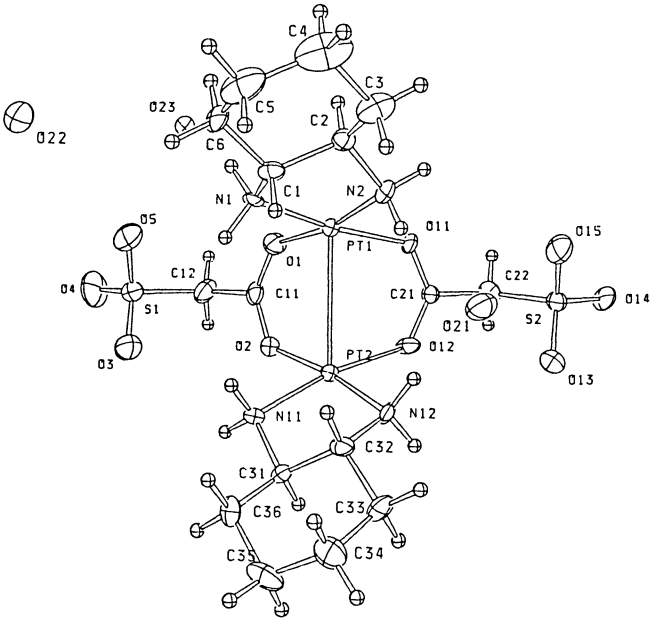

Fig. 1. Molecular structure of the title compound.

References

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2) Nomenclature: (1,1-cyclobutanedicarboxylato)diammineplatinum(II). See references cited in Ref.1.
3) Nomenclature: cis,trans-dichlorodihydroxo-bis(2-aminopropane)platinum(II). See references cited in Ref.1.
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9) Crystallographic data for the title compound: Fw=948.80, orthorhombic, $P2_12_12_1$, a=19.186(4), b=14.577(2), c=9.876(1) Å, V=2762(1) Å^3, Z=4, Dx=2.28, Dm=2.25 g cm^{-3}, R=0.033, wR=0.031 for 2455 independent reflections. Details of the X-ray structure analysis are reported in the following: K. Okude, H. Ichida, T. K. Miyamoto, and Y. Sasaki, submitted to Acta Crystallogr., Sect. C.

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